REMARKS / ARGUMENTS

I. Petition for Reconsideration of Restriction Requirement

The Examiner states that the Decision on Petition was mailed to the applicant on October 13, 2004. This is incorrect. The first time Applicants or Applicants' representative received the Decision was in an e-mail sent by Examiner Baskar on July 25, 2005. By then, the two-month period for reply to the Decision had passed. For the record, we summarize our traversal of the Restriction Requirement.

(a) The DNA and the polypeptide have the same essential structural element

The polypeptide of SEQ ID No: 14 and a nucleic acid encoding it constitute a single inventive concept. Annex B of the Administrative Instructions Under the PCT describes three particular situations for which the method for determining unity of invention contained in Rule 13.2 is explained in detail.

A nucleic acid and the polypeptide it encodes are starting products and final products. There is unity because the DNA and the polypeptide have the same essential structural element, namely that both products share the same polymeric sequence. While nucleic acids and polypeptides are chemically different, the claimed nucleic acids and polypeptides share the same sequence structure, since the initiator codon is described and the nucleic acid sequence is understood to be read in triplets. In particular, part (f)(ii) of the Administrative Instructions states that "the structural element may be a single component or a combination of individual components linked together".

(b) Example 17 of Annex B states that there is unity between protein and DNA

The Examiner is directed to Example 17 of Annex B of the Administrative Instructions Under the PCT. Example 17 states that there is unity between a claim to protein X and a claim to DNA sequence encoding protein X because the protein and the DNA sequence exhibit corresponding special technical features.

(c) The polypeptide and its corresponding antibody share a special technical feature

Example 8 of Annex B of the Administrative Instructions Under the PCT states that there is a special technical feature included in a claim to a plug characterized by feature A and a claim to a socket characterized by corresponding feature A, and that there is unity between these claims. The correspondence between a plug and its socket is equivalent to the correspondence between a protein and an antibody binding to it.

(d) The protein/DNA, methods of manufacturing them and methods of using them share a special technical feature

Example 1 of Annex B of the Administrative Instructions Under the PCT states that there is a special technical feature (substance X) between three categories of claims: (a) a claim to substance X; (b) a claim to a method of manufacturing substance X; and (c) a claim to the use of substance X, and states that the claims therefore have unity.

The method claims are drawn to specific uses of the claimed protein and DNA. The protein/DNA is the special technical feature between these claims and the method claims.

(e) Burden of search

The subject matter of the claims is sufficiently related that a thorough search of the subject matter of any one single independent claim would necessarily encompass a search for the subject matter of the remaining claims. It is respectfully submitted that the search and examination of the entire application could be performed without serious burden. MPEP §803 clearly states that "If the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct or independent inventions." (emphasis added). It is respectfully submitted that this policy should apply in the present application in order to avoid unnecessary delay and expense to Applicants in duplicative examination by the Patent Office.

(f) A special technical feature is present

(i) Over Kalman et al, (GENEMBL, Accession Number AE001641)

The Examiner rejected Applicants' traversal on the grounds that the claims are unified by a single inventive concept. The Examiner stated in the Office Action dated February 28, 2003:

> It is the position of the Office that the expression special technical features shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. However, Kalman et al, (GENEMBL, Accession Number AE001641, 12/1/98; reference A57 on PTOL-1449). (*sic*) Disclose i.e., a nucleic acid molecule comprising SEQ ID NO:1, therefore it does not constitute a special technical feature by definition. Therefore, lack of unity is present. (*Emphasis added*)

Applicants submitted that the revision history of sequence Accession Number AE001641 from the NCBI database, found at http://www.ncbi.nlm.nih.gov/entrez/sutils/girevhist.cgi shows Accession AE001641 was first seen at NCBI on Mar 8 1999 17:32.

The claims relate to SEQ ID NOs:1 and 14 and are fully supported by priority application US 60/113,281 filed December 23, 1998, specifically at Figures 1 and 2 which disclose SEQ ID NOs:1 and 14. The claim date is December 23, 1998. Since Accession AE001641 was first seen after the claim date of the instant application, SEQ ID NOs:1 and 14 do constitute a special technical feature by definition. There is unity present.

(ii) Over Griffais U.S. Patent No. 6,559,294

In the Decision on Petition for Review of Restriction Requirement mailed January 13, 2004, the Commissioner states:

> The technical feature linking groups I-VII appears to be that they are all related to Chlamydia nucleic acids, peptides, antibodies and various methods of using said products. However, Griffais (see the sequence alignment and SEQ ID No. 1 of U.S. Patent No.

> 6,559,294) discloses a nucleic acid comprising a nucleic acid sequence, which encodes an immunogenic fragment of polypeptide comprising 50 (see the sequence alignment) consecutive amino acids, thus meeting the limitations of claim 2(c). Moreover, Griffais has a filing date of 11/23/98, which is before the filing date of the instant application's oldest provisional application, 60/113,280, filed on 12/23/98. Therefore, the technical feature of linking groups I-VII does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art and hence unity of invention is lacking.

In response to the Decision, Applicants submitted a Declaration under 37 CFR § 1.131 of inventor Andrew Murdin. Dr. Murdin declares he had possession of the polypeptide of SEQ ID No:14 and nucleic acids encoding SEQ ID No:14 before Griffais' filing date (November 4, 1998). Note that the relevant date for considering Griffais as prior art is November 4, 1998, not November 21, 1997, because Griffais' 1997 date is a foreign priority claim date and is not relevant under 35 U.S.C. 102(e). See MPEP 706.02(f)(1).

Applicants invented the invention before Griffais. U.S. Patent No. 6,559,294 is not prior art. The technical feature of linking the Restriction Groups does constitute a special technical feature as defined by PCT Rule 13.2 and does define a contribution over the prior art.

(iii) Over Hillier et al. Genome Research 6(9):807-828. 1996

In the Decision on Petition for Review of Restriction Requirement attached to the final Office Action dated October 27, 2005, the Commissioner states that Groups I and II are properly restricted because they do not share a special technical feature. The Commissioner states that the representative claims of Group I are claim 1 (fragment comprising at least 50 amino acids) and claim 3 (sequence anti-sense to the nucleic acid of Group I), and the representative claim of Group II is claim 21 (fragment comprising at least 12 amino acids). The Commissioner states that Hillier et al. anticipates claim 3 because it discloses a sequence which is complementary to nucleotides 370-388 of SEQ ID NO:1.

Applicants point out that claim 1 recites a nucleic acid encoding a "fragment comprising [now amended to --consisting of --] at least 50 consecutive amino acids

from SEQ ID No:14". An antisense sequence according to claim 3 therefore must be at least 150 nucleotides long. Hillier's sequence is only 19 nucleotides and does not antipate claim 3. Nevertheless, solely to advance prosecution, Applicants have canceled claim 3.

Regarding the Commissioner's statement that a sequence of claim 1 encoding a fragment of at least 50 consecutive amino acids from SEQ ID No:14, does not encode the same polypeptide as claim 21, Applicants submit that it is not necessary that SEQ ID No:14 be the common special technical feature. Claims 1 and 21 share the feature that the polypeptide have at least 12 amino acids from SEQ ID No:14 as recited in claim 21.

For the record, Applicants submit that the claims have unity of invention under the PCT.

II. Amendments and Status of Claims

Claims 1, 8, 9, 21, 27 and 28 are amended to recite "a polypeptide which has been modified without loss of immunogenicity, wherein said modified polypeptide is at least 95% identical in amino acid sequence to SEQ ID No:14". This aspect of the claims were canceled by the amendment of April 7, 2004 and now reinstated. Reference to at least 95% identity finds support at least at page 12 lines 24-29 of the specification.

Claims 1, 2, 8, 9, 21, 27 and 28 are amended to recite "consisting of" when referring to the fragments.

Because these amendments and new claims do not introduce new matter, entry thereof by the Examiner is respectfully requested.

Claim 3 is canceled without prejudice or disclaimer. Applicants retain the right to present claims drawn to the cancelled subject matter in a divisional application(s).

The claim dependencies of claims 17 and 25 are amended. As amended, claim 25 depends on claim 1 and should be examined with claim 1.

Claims 1, 2, 4-17, 20-38 and 79-83 will be pending once the amendment has been entered. Claims 20-24, 26-35, 36-38 (in part) are withdrawn. Claims 1, 2, 4-17, 25, 79-83 and 36-38 (in part referring to nucleic acid) are under prosecution.

III. Prior art 35 U.S.C. § 102(e) – US patent 6,559,294 ('Griffais')

The Examiner rejects claims 1, 2, 8, 16, 38(a) (b) and 79-81 under 35 U.S.C. §102(e) as being allegedly anticipated by Griffais. Applicants traverse.

The Examiner states that the 102(e) date for Griffais US patent 6,559,294 is November 21, 1997. The Examiner is incorrect. Griffais' 1997 date is a foreign priority claim date and is not relevant under 35 U.S.C. §102(e). See MPEP 706.02(f)(1). Griffais' 102(e) date is November 4, 1998, and not November 21, 1997. The Declaration filed under 37 CFR § 1.131 of inventor Andrew Murdin shows that the inventors had possession of the invention before the relevant date. Accordingly, withdrawal of the 35 U.S.C. §102(e) rejection over Griffais is requested.

IV. Prior art 35 U.S.C. § 102(b) -- Hillier et al. Genome Research 6(9):807-828. 1996 ('Hillier')

The Examiner rejects claims 1 and 3 as being anticipated by Hillier under 35 U.S.C. § 102(b). Applicants traverse.

The Examiner states that Hillier discloses a sequence which is complementary to nucleotides 370-388 of SEQ ID NO:1. Applicants point out that claim 1 recites a nucleic acid encoding a "fragment consisting of at least 50 consecutive amino acids from SEQ ID No:14". The antisense sequence of claim 3 therefore must be at least 150 nucleotides long. Hillier's sequence is only 19 nucleotides and cannot anticipate

claim 3. Nevertheless, solely to advance prosecution, Applicants have canceled claim 3.

With regard to claim 1, Hillier does not disclose a nucleic acid sequence encoding SEQ ID No:14, an immunogenic fragment consisting of at least 50 consecutive amino acids from SEQ ID No:14; or a polypeptide which has been modified without loss of immunogenicity, wherein said modified polypeptide is at least 95% identical in amino acid sequence to SEQ ID No:14. Withdrawal of the 35 U.S.C. § 102(b) rejection over Hillier is requested.

V. Indefiniteness 35 U.S.C. § 112, 2nd paragraph

The Examiner alleges that "additional polypeptide" renders claim 13 vague and indefinite. Applicants point out that the specification at page 40 lines 21-23, page 27 lines 14-17 and lines 23-26, and page 31 lines 20-27, describes clearly the contemplated additional polypeptide. Withdrawal of the objections under 35 U.S.C. § 112, second paragraph is respectfully requested.

VI. Written description and enablement 35 U.S.C. § 112, 1st paragraph

The Examiner rejects claims 1-17, 36 (a-d), 38 (a-b) and 79-83 under 35 U.S.C. §112, 1st paragraph with respect to the fragments from SEQ ID NOs:1 and 14.

Applicants traverse the rejection as far as they pertain to the amended claims which recite immunogenic fragments consisting of at least 50 consecutive amino acids from SEQ ID No:14, or sequences having at least 95% amino acid identity to SEQ ID NO:14 and retain immunogenicity. For convenience, Applicants will refer to both the fragments and variant sequences as "variants".

Applicants' traversal is based on a number of decisions by the Board of Patent Appeals and Interferences (BPAI) on claims that recite sequence variants or fragments. The BPAI's decisions provide guidance on applying the courts' decisions to claims that recite sequence variants or fragments. Applicants will show how each

decision is pertinent to the instant application, that the Examiner's rejections are contrary to the BPAI, and that the rejections are therefore incorrect.

(a) The specification

Page 12, lines 8-29, states:

> "amino acid sequences are provided which are homologous to any one of SEQ ID Nos:14 to 26 [...] Such a sequence also encompass serotypic variants (defined below) as well as sequences containing deletions or insertions which retain inherent characteristics of the polypeptide such as immunogenicity. [...]
>
> Homologous amino acid sequences include sequences that are identical or substantially identical to SEQ ID Nos:14 to 26. By 'amino acid sequence substantially identical' is meant a sequence that is at least 90%, preferably 95%, more preferably 97%, and most preferably 99% identical to an amino acid sequence of reference."

Page 13, lines 23-27, further states:

> "polypeptides having a sequence homologous to SEQ ID Nos:14 to 26 include naturally-occurring allelic variants, as well as mutants or any other non-naturally occurring variants that retain the inherent characteristics of the polypeptide of SEQ ID Nos:14 to 26."

Page 13, line 28, to page 14, line 19, describes allelic variants, while page 16, lines 9-24, describes non-naturally occurring homologs and fragments. Page 20, line 20, to page 21, line 6, describes that masked epitopes can be revealed by making internal deletions to the sequence, and page 37, lines 7-17, describes the possible substitutions. Page 21, line 7, to page 22, line 26, describes fusion polypeptides, especially those having an adjuvant component or a strong T-cell or B-cell epitope to optimize the immune response against Chlamydia infection.

Page 18, line 14, to page 19, line 7, describes use of fragments and variants of protein immunogens in vaccines. Specifically, lines 20-32 of page 18 asserts utility for fragments since "all that is required to induce an immune response to a protein is a small (*e.g.*, 8 to 10 amino acid) immunogenic region of the protein." Furthermore, "various short synthetic peptides corresponding to surface-exposed antigens of pathogens other than *Chlamydia* have been shown to be effective vaccine antigens against their respective pathogens".

Page 42, line 16, to page 43, line 10, describes using the polypeptides and fragments to generate antibodies. Page 43, line 10, to page 44, line 24, describes using the polypeptides and fragments for Chlamydia diagnostic applications. Page 20, lines 1-19, describes using computer-assisted analysis to identify probable surface-exposed, antigenic regions. Page 14, lines 12-19, describes how Chlamydia MOMPs are tolerant of amino acid variations. Page 16, line 25, to page 18, line 13, describes tests for determining, without undue experimentation, whether a particular homolog of SEQ ID NO:14 may be useful in the prevention or treatment of Chlamydia infection. Page 37, line 18, to page 39, line 18, describes how to identify variants for cross-reactive antigenicity. Page 17, line 7, to page 18, line 13, describes a mouse model for testing protective immunity against Chlamydia infection.

(b) The Examiner on written description

The Examiner states: "[The] broadly claimed nucleic acid sequence which encodes a polypeptide SEQ ID NO:14 variants/fragments, a nucleic acid comprising 38, 100 consecutive nucleic acids, a nucleic acid sequence encoding an immunogenic fragments of 50 or 12 consecutive amino acids and a method of preventing infection using such nucleic acid is not set forth in this specification."

The Examiner states that "The 98kD outer membrane protein is uncharacterized by this specification and is not asserted to belong to any known family of proteins. [...] The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of a representative number of polynucleotides encoding a representative number of 98kD polypeptides".

The Examiner states that "With the exception of an isolated polynucleotide comprising SEQ ID NO:1 and an isolated polynucleotide comprising of a nucleotide sequence encoding SEQ ID NO:14, fragments thereof and associated, vectors, vaccines, fusions etc dependent thereon, the skilled artisan cannot envision the

contemplated nucleotide sequences by the detailed chemical structure of the claimed polynucleotides".

(c) The MPEP on written description

Section 2163.04 of the MPEP places the burden on the Examiner with regard to the written description requirement:

> "A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97.
>
> [...]
>
> In rejecting a claim, the examiner must set forth express findings of fact which support the lack of written description conclusion [...]. These findings should [...] [e]stablish a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. A general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description."

(d) The BPAI on written description

(i) *Ex parte Sun*, Appeal No. 2003-1993, Application No. 09/470,526 (Jan 20, 2004)

The Examiner in *Ex parte Sun* rejected a claim directed to an isolated wee1 nucleic acid comprising a wee1 polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1. The examiner argued that the "specification does not set forth what specific structural or physical features define the claimed isolated nucleic acids," that one skilled in the art "could not predict the structure and function" of such variants, and that the specification did not teach a single representative species with 80% identity and Wee1 function.

The Board stated that to satisfy the written description requirement, it is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that applicants invented the claimed subject matter. Thus, the fact that the specification does not specifically teach the structure of a species with 80% identity and WEE1 function is not dispositive of the written description issue. The Board cited *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002).

The specification in *Ex parte Sun* describes a polynucleotide structure that encodes SEQ ID NO:2 and provides an example of how to screen for WEE1 activity. The Board stated that such a description constitutes sufficiently detailed, relevant identifying characteristics consistent with Enzo (*supra*). The Board further states that the examiner has failed to indicate why one of ordinary skill in the art, in possession of the polynucleotide that encodes a polypeptide of SEQ ID NO:2, would be unable to recognize that the inventors have invented the subject matter within the scope of the claims, including homologues sharing structural features with the specifically claimed and disclosed structures. The Board reversed the rejection for lack of written description.

Relevance: The facts presented in *Ex parte Sun* are analogous to the present application. Applicants' claims recite a sequence having at least 95% sequence identity to SEQ ID NO:14. The present specification describes how to screen for variants that retain immunogenicity. The Examiner has not indicated why a skilled person would be unable to recognize that the inventors have invented the variants sharing structural features with the specific structure SEQ ID NO:14. The claims therefore have sufficient written description support.

(ii) *Ex parte Meyers*, Appeal No. 2003-1820, Application No. 09/464,039 (Aug. 31, 2004)

The examiner in *Ex parte Meyers* rejected a claim drawn to a nucleic acid having a sequence encoding a polypeptide having dehydrogenase activity and having

at least 70% sequence identity with SEQ ID NO:8. The examiner states that the specification fails to disclose any functional variant of human alcohol dehydrogenase.

The applicant argued that Pfam analysis could be used to predict whether the variant sequences possessed dehydrogenase activity. (Pfam is a database of protein domain families and contains curated multiple sequence alignments for each family, as well as profile hidden models for finding these domains in new sequences.) The Board agreed, finding "no evidence on this record that the Pfam analysis cannot be used to assign a function to a protein.". The Board pointed out that the examiner has the initial burden of establishing insufficient written description, but failed to present evidence to demonstrate that one of skill would doubt the credibility of applicant's assertion of dehydrogenase function. The Board reversed the rejection for lack of written description.

Relevance: The facts presented in *Ex parte Meyers* are analogous to the present application. Applicants' claims recite a sequence having at least 95% sequence identity to SEQ ID NO:14 and retaining immunogenicity. The present specification describes how to screen for variants that retain immunogenicity, and also describes computer-assisted methods to identify probable surface-exposed antigenic regions. The Examiner has not indicated why this analysis cannot be used to assign functional immunogenicity to a polypeptide. The Examiner has not presented evidence to demonstrate that one of skill would doubt the credibility of applicant's assertion of immunogenic function. The claims therefore have sufficient written description support.

(iii) *Ex parte Bandman*, Appeal No. 2004-2319, Application No. 09/915,694 (Jan. 6, 2005)

The examiner in *Ex parte Bandman* rejected claims encompassing an isolated polynucleotide encoding a polypeptide comprising a naturally occurring amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1. The examiner contends that the specification failed to sufficiently describe the invention because it provides only a single representative species—an isolated

polynucleotide consisting of SEQ ID NO: 2. The examiner asserts that "[t]here is no disclosure of any particular structure to function/activity relationship in the single disclosed species."

The Board reviewed the relevant jurisprudence, specifically *The University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1998) and *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1602 (Fed. Cir. 2002). The Board stated that in this case, the complete structure of the polynucleotide of SEQ ID NO: 2 has been described, and the genus is limited to a polynucleotide comprising a naturally occurring sequence having at least 95% identity to SEQ ID NO: 2. In addition, the complete structure of the polypeptide of SEQ ID NO: 1 has been described, and the genus is limited to polypeptides comprising a naturally occurring amino acid sequence having at least 95% identity to SEQ ID NO: 1. The examiner asserts that the specification provides no disclosure of any particular structure to function/activity relationship in the single disclosed species, but has not adequately explained and/or provided evidence to support that assertion. The Board reversed the rejection for lack of written description.

Relevance: The facts presented in *Ex parte Bandman* are analogous to the present application. Applicants' claims recite a sequence having at least 95% amino acid sequence identity to SEQ ID NO:14. The Examiner has not adequately explained and/or provided evidence to support the contention that the specification provides no disclosure of any particular structure to function/activity relationship. The claims therefore have sufficient written description support.

(iv) *Ex parte Chung*, Appeal No. 2004-2201, Application No. 09/788,476 (Nov. 22, 2004)

The examiner in *Ex parte Chung* rejected a claim drawn to a nucleotide sequence having at least about 60% similarity to the full length of a reference sequence and that hybridizes to the reference sequence under specified conditions. The examiner also rejected a claim reciting a corresponding mRNA that is differentially or preferentially expressed in a specific disease tissue. The examiner

contends that the claim does not comply with the written description requirement because the expression of the claimed nucleic acid is "not function associated with the structure but a reaction of the human body to certain stimuli, in the instant case the development of HCC or pancreatic adenocarcinoma."

The Board pointed out that the examiner has not provided an analysis of why the function set forth in the rejected claim is not an adequate identifier of the claimed genus of nucleic acids, and so has not met the initial burden of establishing insufficient written description. The Board reversed the rejection for lack of written description.

Relevance: The facts presented in *Ex parte Chung* are analogous to the present application. Applicants' claims recite a sequence having at least 95% sequence identity to SEQ ID NO:14. As is the case in *Ex parte Chung*, the claims recite a functional limitation ("immunogenic fragment" and "without loss of immunogenicity") that relates to a reaction of the body rather than the biological activity of the sequence. The Examiner has not provided an analysis of why this function is not an adequate identifier of the claimed genus of sequences. The Examiner requires that the 98 kD outer membrane protein be asserted as belonging to a known family variants and that the variants be characterized this way, but has not stated why they cannot be characterized by their immunogenic function. The Examiner therefore has not met the initial burden of establishing insufficient written description. The claims therefore have sufficient written description support.

(v) *Ex parte McElroy*, Appeal No. 2003-0936, Application No. 09/352,806 (Aug. 29, 2003)

The examiner in *Ex parte McElroy* rejected claims reciting an isolated nucleic acid comprising a maize GRP promoter comprising at least 95 contiguous bases of SEQ ID NO:1. The examiner contends that although the specification describes every fragment of at least 95 contiguous nucleotides from the 3536 nt of SEQ ID NO:1, it does not identify which would work as promoters. The examiner requires that the description allow those skilled in the art to recognize what regions of SEQ ID NO:1

need be retained for promoter function. Specifically the examiner argues that what is required is a description of which structural features are necessary to retain function, or a description of a representative number of fragments having promoter function so that a skilled person can recognize the promoter-retaining characteristics of SEQ ID NO:1 fragments.

The Board states that the specification describes SEQ ID NO:1 by naming its 3536 contiguous nucleotides. In so doing, it *prima facie* described each and every isolated 95, 110, 125, 250, 400, 750, 1000, 1500, 2000, 2500, and 3000 contiguous nucleotide segment of the 3536 contiguous nucleotides of SEQ ID NO:1 comprising a functional maize GRP promoter. The Board reviewed the relevant jurisprudence: *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991), *The University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997)), *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002), and *Evans v. Eaton*, 20 U.S. (7 Wheat.) 356 (1822). The Board found that the promoter fragments as claimed are precisely defined in terms of structure, formula, chemical name, and function. The Board reversed the rejection for lack of written description.

Relevance: The facts presented in *Ex parte McElroy* are analogous to the present application. Applicants' claims recite a sequence which is a subsequence of a specifically disclosed whole. As is the case in *Ex parte McElroy*, the specification describes SEQ ID NOs:1 and 14 by naming their specific sequences and in so doing, there is *prima facie* description of each and every fragment within the whole sequence. The claims therefore have sufficient written description support.

(vi) *Ex parte Friedberg*, Appeal No. 2004-2314, Application No. 09/971,101 (Nov. 17, 2004)

The Examiner in *Ex parte Friedberg* rejected claims to an isolated and purified polypeptide comprising at least 10 contiguous amino acids of SEQ ID NO:2 or 4. The examiner concedes that polypeptides consisting of contiguous amino acids from SEQ ID NO: 2 or 4 are fully described. Nevertheless, the examiner contends

that polypeptides comprising the contiguous amino acids are not fully described when additional characteristics such as function are not set out in the specification.

The Board pointed out that written description does not require a description of the complete structure of every species within a chemical genus, citing *Utter v. Hiraga*, 845 F.2d 993, 998, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988). The specification provides the complete structure of the fragments since the complete sequence of SEQ ID NO:2 and 4 is described and the fragments are merely subsequences of the whole. The Board considered *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) and *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002) with respect to the claimed sequences that comprise at least 10, 20, 30, 40, 75, or 100 contiguous amino acids of SEQ ID NO:2 or SEQ ID NO:4. The Court in *Lilly* held that a genus could be described via "recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus". The court in *Enzo* held that such a description could take the form of "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." The Board concluded that, given the complete structure of SEQ ID NO:2 and 4, the structural features that are common to the polypeptides of the claimed genus are the at least 10 contiguous amino acids. The examiner has not adequately explained why this degree of structural similarity is inadequate to "constitute a substantial portion of the genus," as required by *Lilly*. The Board reversed the rejection for lack of written description.

Relevance: The facts presented in *Ex parte Friedberg* are analogous to the present application. Applicants' claims recite immunogenic fragments which are subsequences of a specifically disclosed polypeptide sequence. The specification provides the complete structure of the fragments since the complete sequences of SEQ ID NOs:1 and 14 are described and the fragments are merely subsequences of the whole. The structural features that are common to the polypeptides of the claimed genus are the at least 12 contiguous amino acids. The Examiner has not adequately explained why this degree of structural similarity is inadequate to "constitute a

substantial portion of the genus," as required by *Lilly*. The claims therefore have sufficient written description support.

(e) The Examiner on enablement

The Examiner states that protein chemistry is an unpredictable area and refers to specific examples to show that changes in sequence leads to unpredictable changes in activity. The specific examples cited by the Examiner are: peptide hormones (Rudinger in "Peptide Hormones" edited by Parsons J.A., University Park Press, June 1976, pages 1-6), fibroblast growth factor (Burgess et al. J. Cell Biol. 111:2129-2138, 1990), growth factor alpha (Lazar et al. Mol. Cell. Biol. 8(3):1247-1251, 1988), and the B subunit of cholera toxin (Jobling & Holmes. Mol. Microbiol. 5(7):1755-1767, 1991).

The Examiner states that the specification provides no working examples demonstrating enablement for the variants and doubts the utility of the claims. The Examiner further asserts "The specifications does not ensure that the protein or its variants would be able to successfully generate a protective immune response to treat or prevent an infection", and cites a number of references in support of lack of utility: Allen et al. J. Immun. 1991. 147:674-679, Battereiger et al. 1996. Infect. Immun. 64:2839-2841, and Murdin et al. 2000. J. Infect. Diseases 181(Suppl. 3):S552-S557. The Examiner further asserts that "At the time of filing, gene therapy of Chlamydia using the direct administration of DNA was considered to be highly unpredictable." The Examiner cites Verma et al. 1997. Nature 389:239, and Miller et al. 1995. FASEB J. 9:190-199.

(f) The MPEP on enablement

Section 2164.04 of the MPEP places the burden on the Examiner with regard to the enablement requirement:

> "[T]he examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must

provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370.

According to *In re Bowen*, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. This standard is applicable even when there is no evidence in the record of operability without undue experimentation beyond the disclosed embodiments."

(g) Applicants' submissions about the state of the art

With respect to the references Allen et al. J. Immun. 1991. 147:674-679, Battereiger et al. 1996. Infect. Immun. 64:2839-2841, and Murdin et al. 2000. J. Infect. Diseases 181(Suppl. 3):S552-S557, Applicants submit a declaration under 37 C.F.R. §1.132 from inventor Murdin. Dr. Murdin declares that the publication does not relate to his personal knowledge of scientific results obtained by Aventis Pasteur Limited, in the field of DNA vaccines against Chlamydia. Rather, the publication relates only to general knowledge known to skilled workers who do not have access to scientific results obtained at Aventis Pasteur Limited. In Dr. Murdin's opinion, the results obtained at Aventis Pasteur Limited indicate that at least one true candidate exists against Chlamydia, i.e. the vaccine which is subject of the present application. Therefore, Allen et al. J. Immun. 1991. 147:674-679, Battereiger et al. 1996. Infect. Immun. 64:2839-2841, and Murdin et al. 2000. J. Infect. Diseases 181(Suppl. 3):S552-S557 do not accurately show the state of the art as it pertains to the instant application.

With respect to Verma et al. 1997. Nature 389:239, and Miller et al. 1995. FASEB J. 9:190-199, Applicants submit that the Examiner's assertions about gene therapy do not apply to DNA vaccines. A search on the internet using the words "DNA vaccine" and "clinical trial" results in numerous hits. Applicants attach a review article Ribas et al. 2003. J. Clin. Oncology 21(12):2415-2432 which lists clinical trials for cancer vaccines; see Tables 2 and 3 on pages 2422-2425, in particular the listing of naked DNA vaccines and viral vector vaccines. The Examiner should note that these DNA vaccines had been in Phase I, II or III trial as of 2003, and so it is highly likely that they were developed and shown to be feasible as of 1999 (the filing date). Applicants also attach a press release "Vical License Nakes DNA Technology ...", which states "Aventis Pharma initiated a clinical trial in 1999 testing naked DNA delivery of a gene encoding an angiogenic growth factor in patients with critical limb ischemia". It is therefore evident that DNA vaccines were feasible before the filing date of the instant application.

(h) <u>The BPAI on enablement</u>

(i) *Ex parte Sun*, Appeal No. 2003-1993, Application No. 09/470,526 (Jan. 20, 2004)

The Examiner in *Ex parte Sun* rejected a claim directed to an isolated wee1 nucleic acid comprising a wee1 polynucleotide having at least 80% identity to the entire coding region of SEQ ID NO:1. The examiner argues that the specification does not reasonably provide enablement for such variants because it does not disclose any specific structural or functional characteristics of any isolated nucleic acid variants. The Examiner also argues that the specification does not disclose any examples of how to make a transgenic host cell or plant comprising such variants or provide any definitive evidence that introducing such variants into a plant will result in an alteration of the plant's phenotype.

The Board pointed out that only objective enablement is required and so it is irrelevant whether this teaching is provided through broad terminology or illustrative

examples (citing *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)). The Board considered whether the examiner has advanced an acceptable reasoning inconsistent with enablement and concluded the examiner has not met his burden. The Board reversed the rejection for lack of enablement.

Relevance: The facts presented in *Ex parte Sun* are analogous to the present application. Applicants' claims recite a sequence having at least 95% sequence identity to SEQ ID NO:14. The present specification describes how to screen the variants for those that retain immunogenicity. It is irrelevant whether an enabling disclosure is provided through broad terminology or illustrative examples. The Examiner has not advanced an acceptable reasoning as is required for meeting the burden of showing non-enablement. The claims are therefore enabled.

(ii) *Ex parte Meyers*, Appeal No. 2003-1820, Application No. 09/464,039 (Aug. 31, 2004)

The examiner in *Ex parte Meyers* rejected a claim drawn to a nucleic acid having a sequence encoding a polypeptide having dehydrogenase activity and having at least 70% sequence identity with SEQ ID NO:8. The Examiner argues that the variants are not enabled because the specification does not teach "what additional sequences may be added, deleted or substituted to those specifically disclosed, such that asserted [sic] utility discussed in the section 101 rejection above would be recognized as specific and/or substantial." The applicant argues that Pfam analysis could be used to predict whether the variant sequences possessed dehydrogenase activity, but the Examiner asserts that the recited SEQ ID NO(s) are simply computer-generated hypotheses with no established biological function.

The Board agreed with the applicant, finding "no evidence on this record that the Pfam analysis cannot be used to assign a function to a protein.". The Examiner offers no evidence to suggest that Pfam analysis is not an art-accepted method of determining protein function.

The Examiner asserts that the specification fails to show a single working example that establishes the alcohol dehydrogenase function of the polypeptide, such as by substantial homology and/or functional assay of the protein. The Examiner further asserts "[i]t is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if..."

The Board pointed out that there is no rule of law that requires the specification to contain a working example, citing *In re Strahilevitz*, 668 F.2d 1229, 1232, 212 USPQ 561, 563 (CCPA 1982). The Board said the Examiner's reference to general knowledge does not fulfil his obligation to cite references to support his conclusions, citing *In re Lee*, 277 F.3d 1338, 1344, 61USPQ2d 1430, 1434 (Fed. Cir. 2002).

The Examiner indicates that to enable the invention, the specification must disclose the role of the polypeptides in a disease. The Board disagreed, reminding the Examiner that "[t]he enablement requirement is met if the description enables any mode of making and using the invention." citing *Johns Hopkins Univ. v. CellPro Inc.*, 152 F. 3d 1342, 1361, 47 USPQ2d 1705, 1714 (Fed. Cir. 1998). Since the specification describes uses unrelated to disease applications, the Board has no reason to doubt applicant's presumptively enabled specification (citing *In re Marzocchi*, 439 F 2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

The Board concluded the Examiner failed to meet his burden of providing the evidence necessary to establish a lack of an enabling description and reversed the rejection for lack of enablement.

Relevance: The facts presented in *Ex parte Meyers* are analogous to the present application. Applicants' claims recite a sequence having at least 95% amino acid sequence identity to SEQ ID NO:14 and retaining immunogenicity. The present specification describes how to screen the variants for those that retain immunogenicity, and also describes computer-assisted methods to identify probable surface-exposed antigenic regions. The Examiner has not indicated why these screening method and analysis cannot be used to assign functional immunogenicity to

a polypeptide, nor why they are not an art-accepted methods of determining immunogenic function.

Although the Examiner cites references purporting to show that changes in sequence leads to unpredictable changes in activity, the specific examples cited by the Examiner (peptide hormones, fibroblast growth factor, growth factor alpha, and the B subunit of cholera toxin) do not relate to the immunogenic function recited in the claims. These citations merely indicate general knowledge and do not meet the burden of showing non-enablement. As regards the Examiner's remaining citations as evidence of state of the art, Applicants refute the Examiner's assertions (see above section "Applicants' submissions about the state of the art"). The claims are therefore enabled.

(iii) *Ex parte Bandman*, Appeal No. 2004-2319, Application No. 09/915,694 (Jan. 6, 2005)

The examiner in *Ex parte Bandman* rejected claims encompassing an isolated polynucleotide encoding a polypeptide comprising a naturally occurring amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 1. The examiner argues that "The amount of experimentation to make the claimed polynucleotide is enormous and undue and entails selecting specific nucleotides to change (deletion insertion, substitution, or combinations thereof) in any polynucleotide to make a polynucleotide encoding a polypeptide comprising an amino acid sequence that is at least 95% identical to SEQ ID NO: 1 or selecting specific nucleotides to change (deletion, insertion, substitution, or combinations thereof) in the nucleotide sequence of SEQ ID NO: 2 to make a polynucleotide that has a nucleotide sequence that is at least 95% identical to SEQ ID NO: 2 and determining by assays whether the encoded polypeptide has malate dehydrogenase activity."

The Board agreed with the applicants that the specification is enabled because nature will have determined the appropriate amino acid sequences through natural selection. The Board pointed out that the need for some experimentation is not fatal; the issue is whether the amount of experimentation required is 'undue', citing *In re*

Vaeck, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). Some experimentation, even a considerable amount, is not "undue" if, e.g., it is merely routine, or if the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed, citing *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Board pointed out that the examiner has not explained and/or provided evidence why a naturally occurring polypeptide that is at least 95% identical to SEQ ID NO: 1 would not have malate dehydrogenase activity. The examiner bears the initial burden of showing nonenablement, citing *In re Wright*, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993), and has not met it. The Board reversed the rejection for lack of enablement.

Relevance: The facts presented in *Ex parte Bandman* are analogous to the present application. Applicants' claims recite a sequence having at least 95% amino acid sequence identity to SEQ ID NO:14. The Examiner has not explained and/or provided evidence why a variant that is at least 95% identical to SEQ ID NO:14 would not retain immunogenicity. The Examiner bears the initial burden of showing nonenablement and has not met it. The claims are therefore enabled.

(iv) *Ex parte Chung*, Appeal No. 2004-2201, Application No. 09/788,476 (Nov. 22, 2004)

The examiner in *Ex parte Chung* rejected a claim drawn to a nucleotide sequence having at least about 60% similarity to the full length of a reference sequence and that hybridizes to the reference sequence under specified conditions. The examiner also rejected a claim reciting a corresponding mRNA that is differentially or preferentially expressed in a specific disease tissue. The examiner focused on the purported need to screen a "large quantity of clinical samples" in order to enable the claim throughout its scope.

The Board cited *PPG Indus., Inc. v. Guardian Indus. Corp.*, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996) (citations omitted):

> In unpredictable art areas, this court has refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make

> and use other potential embodiments across the full scope of the claim. Enablement is lacking in those cases, the court has explained, because the undescribed embodiments cannot be made, based on the disclosure in the specification, without undue experimentation. But the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' The Patent and Trademark Office Board of Appeals summarized the point well when it stated:
>
> > The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

The Board pointed out that the examiner has not provided an analysis of why the amount of work required to practice the invention throughout its scope would be considered undue instead of routine. It is insufficient for an examiner to merely point out that it is necessary to "screen a large quantity of clinical samples." The Board reversed the rejection for lack of enablement.

Relevance: The facts presented in *Ex parte Chung* are analogous to the present application. The present claims recite a sequence having at least 95% sequence identity to SEQ ID NO:14. As is the case in *Ex parte Chung*, the claims recite a functional limitation ("immunogenic fragment" and "without loss of immunogenicity") that relates to a reaction of the body rather than the biological activity of the sequence. The Examiner has not provided an analysis of why the amount of work required to practice the invention throughout its scope would be considered undue instead of routine. The claims are therefore enabled.

(v) *Ex parte McElroy,* Appeal No. 2003-0936, Application No. 09/352,806 (Aug. 29, 2003)

The examiner in *Ex parte McElroy* rejected claims reciting an isolated nucleic acid comprising a maize GRP promoter comprising at least 95 contiguous bases of SEQ ID NO:1. The examiner asserts that the specification does not provide sufficient

structural and functional information for a skilled person to recognize which fragments would have promoter function.

The Board stated that it is legal error to require that an applicant disclose a common chemical structure essential for functional activity. The Board pointed out that (1) it may not be necessary to disclose, or even know, the chemical structure essential for functional activity to enable a skilled person to make and use the full scope, and (2) there may not be a common chemical structure essential for functional activity. Some experimentation is permissible as long as it is not "undue". Citing *In re Angstadt*, 190 USPQ 214, 218-219 (CCPA 1976), the Board determined that the examiner sets too high a standard in requiring that the level of guidance be high enough for there to be reasonable certainty of the experimental outcome, since that would make all experimentation undue. The standard should be that the amount of experimentation be reasonable, even if the end result is uncertain. The Board reversed the rejection for lack of enablement.

Relevance: The facts presented in *Ex parte McElroy* are analogous to the present application. Applicants' claims recite a sequence which is a subsequence of a specifically disclosed whole, and which is immunogenic. The present specification describes how to screen the fragments for immunogenicity, and also describes computer-assisted methods to identify probable surface-exposed antigenic regions. As the Board pointed out, (1) it may not be necessary to disclose, or even know, the chemical structure essential for functional activity to enable a skilled person to make and use the full scope, and (2) there may not be a common chemical structure essential for functional activity. A reasonable amount of experimentation is permissible even if the end result is uncertain. The Examiner has not indicated why the screening method and computer-assisted analysis cannot be used to assign functional immunogenicity to a polypeptide, nor why they are not an art-accepted methods of determining immunogenic function. Applicants submit that given these teachings, the amount of experimentation is reasonable. The claims are therefore enabled.

(vi) *Ex parte Friedberg*, Appeal No. 2004-2314, Application No. 09/971,101 (Nov. 17, 2004)

The Examiner in *Ex parte Friedberg* rejected claims to an isolated and purified polypeptide comprising at least 10 contiguous amino acids of SEQ ID NO:2 or 4. The examiner contends that the specification is not enabling because it lacks guidance for using the majority of the claimed genus of polypeptides. The examiner relies on a reference on protein structure prediction to show that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) is not well understood and is not predictable.

The Board disagreed with the examiner, citing *Johns Hopkins Univ. v. CellPro Inc.*, 47 USPQ2d 1705, 1714 (Fed. Cir. 1998) for the proposition that "The enablement requirement is met if the description enables any mode of making and using the invention." The examiner mistakenly assumed that the required utility is pol κ activity. The specification enabled use of pol κ fragments, including those without pol κ activity, for making anti-pol κ antibodies. In this regard, the examiner fails to explain how the reference on protein structure prediction relates to using the claimed polypeptides to prepare antibodies. The Board reversed the rejection for lack of enablement.

Relevance: The facts presented in *Ex parte Friedberg* are analogous to the present application. Applicants' claims recite immunogenic fragments from SEQ ID NO:3 and 4. The present specification asserts utility for fragments, stating that "all that is required to induce an immune response to a protein is a small (*e.g.*, 8 to 10 amino acid) immunogenic region of the protein" and "various short synthetic peptides corresponding to surface-exposed antigens of pathogens other than *Chlamydia* have been shown to be effective vaccine antigens against their respective pathogens". The specification further describes using fragments to generate antibodies and for Chlamydia diagnostic applications.

As the Board pointed out, the enablement requirement is met if the description enables any mode of making and using the invention. It is not required that the

variants function as part of any 98kD protein family. The instant specification enables use of the fragments for making antibodies. The Examiner cites specific references purporting to show that changes in sequence leads to unpredictable changes in activity, but these do not relate to the immunogenic function recited in the claims, or to making antibodies as described in the specification. The claims are therefore enabled.

Withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

VII. Concluding Remarks

In view of the above amendments and remarks, reconsideration and favorable action on all pending claims are respectfully requested. If any questions or issues remain, the Examiner is invited to contact the undersigned at the telephone number set forth below so that a prompt disposition of this application can be achieved.

If a fee is required for an extension of time which is not accounted for, such an extension is requested and the U.S.P.T.O. is authorized to withdraw from our Deposit Account Number 19-0741 any fee required.

Respectfully submitted,

Date: Feb 27, 2006

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